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The role of maternal diet on offspring hyperinsulinaemia and adiposity after birth: a systematic review of randomised controlled trials

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Review

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Abstract

In utero diet may be directly related to the risk of fetal hyperinsulinaemia and offspring metabolic health. This review examines the relationship between maternal dietary exposures and sub-clinical fetal hyperinsulinaemia and neonatal adiposity. Articles were identified in MEDLINE, Web of Science, Cochrane Controlled Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, SCOPUS, and SPORTDiscus (September 2019–March 2021) using the preferred reporting items for systematic reviews and meta-analyses guidelines. PROSPERO registration ID CRD42020146453. Studies were selected by two independent reviewers. Randomised controlled trials (RCT) involving a dietary intervention with pregnant women (healthy pregnancy, gestational diabetes mellitus and obesity) and reporting fetal cord-blood insulin, c-peptide, glucose or adiposity estimates were included. One author extracted all information on main study characteristics and outcomes. Risk of bias was assessed using the Cochrane Collaboration's bias risk assessment tool. A total of 733 articles were identified. Fourteen articles from 11 RCTs (3614 participants) were included. Studies reviewed showed no specific effect of maternal diet on neonatal cord blood insulin, c-peptide or glucose levels. Infants born to mothers who followed a low glycaemic load (GL) had lower skin fold thickness compared to controls. Interventions that provided individualised nutrition counselling to women with obesity or previous infant born > 4 kg were also associated with lower adiposity. The studies reviewed suggest that lifestyle-based dietary interventions to improve glycaemia (low GL) have a protective effect against excess adiposity. Future studies should incorporate multi-modal interventions with dietary counselling to support lifestyle changes throughout gestation and include assessments of maternal insulin resistance at recruitment.

Background

Maternal insulin resistance during pregnancy is a normal and essential adaptation that ensures adequate nutrition to support the life of a growing fetus.[1] Women with reduced pregravid insulin sensitivity compensate with an increased insulin response (hyperinsulinaemia), which affects early placental growth and gene expression. Maternal metabolism undergoes ongoing changes in insulin sensitivity mediated by circulating placental factors that drive excessive nutrient availability.[2] When augmented by maternal insulin resistance, this increases the risk of many complications for both the mother and neonate.[3] The global rise of insulin resistance syndromes such as obesity and polycystic ovarian syndrome among women of childbearing age has led to a growing interest in lifestyle-based strategies to mitigate the complications associated with maternal metabolic demands.[1] Maternal hyperinsulinaemia is associated with a milieu of metabolic derangements, including hyperglycaemia, hyperlipidaemia and inflammation in the mother.[4] These abnormalities are associated with an increased risk of developing gestational diabetes mellitus (GDM), hypertensive disorders, non-alcoholic fatty liver disease, cardiomyopathy, birthing complications,[1,5] as well as a life-long increased risk of metabolic syndrome and type 2 diabetes.[6]

Maternal hyperinsulinaemia is known to have transgenerational impacts that beget childhood metabolic dysfunction. These genetic and epigenetic exposures *in utero* have lasting effects on the offspring's later life metabolic health.[1,7] Maternal insulin resistance has been shown to alter placental and fetal metabolism in ways that can lead to fetal overgrowth, endothelial dysfunction, and neurological disorders in the neonate.[8] Furthermore, alterations in the maternal insulin/insulin-like growth factor axis have been demonstrated in GDM pregnancies,[9] and are thought to have an important role in mediating fetal outcomes.[10,11]

The fetal response to maternal overnutrition is fetal hyperinsulinaemia, which mediates developmental pathways involved with growth, body composition, and mitochondrial function in the offspring.[1] In pregnancies complicated by diabetes mellitus, the maternal hyperglycaemia-fetal hyperinsulinaemia response leads to an increased risk of developmental and metabolic complications such as neonatal hypoglycaemia and macrosomia (infant born > 4 kg). Although interventions that reduce occurrence of adverse neonatal events are well-established in GDM pregnancies particularly,[12] there is growing interest in the long-term developmental impacts of *in utero* hyperinsulinaemia for infants born to women with normal-to-borderline hyperglycaemia.

Evidence from the largest blinded multinational study on adverse pregnancy outcomes, the hyperglycaemia and adverse pregnancy outcome (HAPO) cohort study (23,316 participants) highlighted the breadth at which fetal hyperinsulinaemia can be observed in pregnancies across a spectrum of clinical and sub-clinical maternal hyperglycaemia.[13] The HAPO study showed an independent and continuous linear relationship between non-diabetic hyperglycaemia in pregnancy and cord serum c-peptide. Newborns with higher cord serum c-peptide (>90th percentile) were also larger and fatter and had a higher clinical incidence on neonatal hypoglycaemia.[14] Cord c-peptide has repeatedly been found to mediate the relationship between maternal body mass index (BMI) and infant size,[15] and maternal hyperglycaemia and childhood adiposity,[16] thus providing a plausible causal link between *in utero* exposures and later life metabolic diseases.[17] This suggests *all* women at risk of fetal hyperinsulinaemia, such as those with obesity, may benefit from interventions to mitigate excursions in nutrient excess, not only those affected by GDM.

Various dietary interventions have been implicated for reducing the risk of adverse outcomes in GDM pregnancies.[18] A meta-analysis by Yamamoto *et al.*[19] of 18 studies showed various modified dietary interventions including the low glycaemic index (GI) and the dietary approaches to stop hypertension (DASH) diet were associated with improved maternal glycaemia, lower neonatal birth weight and reduced macrosomia. Outside of GDM, various dietary interventions for pregnant women with overweight or obesity have been implicated for limiting gestational weight gain and preventing GDM incidence.[20] Among them, effective dietary interventions involve nutrient or energy restriction alongside behavioural and physical activity components. It is plausible that such interventions which reduce GDM occurrence also create a more favourable metabolic environment for fetal development.

Despite cord blood metabolites providing a promising marker of *in utero* exposures and infant metabolic development health, to our knowledge, there have been no systematic reviews published in the last 5 years that summarise current evidence from dietary studies on fetal insulin metabolism outcomes. Since it is unclear whether cord-blood metabolites, specifically insulin and c-peptide, from non-GDM pregnancies can provide a sensitive indicator of sub-clinical *in utero* exposures, excess infant adiposity is proposed to be both a plausible and measurable mediator of transgenerational metabolic dysfunction.[21,22] Neonatal adiposity appears to be tightly linked to *in utero* fetal insulin levels,[23] and altered cord-blood metabolites; reflective of altered fatty acid oxidation and mitochondrial dysfunction.[24]

For this review, we aimed to examine the relationship between different dietary interventions in metabolically healthy and high-risk pregnant populations and sub-clinical fetal hyperinsulinaemia measured as cord blood metabolites and neonatal adiposity.

Table 1. Categories for formulation of the research question for a systematic review on effects of dietary interventions and associations of dietary intake with neonatal outcomes

Category	Result
Population	Pregnant adult women (>18 years) and neonate up to 6 months of age
Intervention/ exposure	Dietary intervention (intervention studies)
Comparison	Control group (e.g. standard care as part of randomised controlled trial) or a different dietary intervention
Outcome	Neonatal cord blood insulin, c-peptide, glucose and neonatal adiposity up until 6 months of age.
Study designs	Intervention studies

Methods

This review was prepared in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines.[25] The review protocol was registered in the PROSPERO International prospective register of systematic reviews (ID CRD42020146453). The population, intervention, comparator, outcomes and study design criteria, used to define the research question and to select the studies, are presented in Table 1.

Search strategy

The literature search was performed using MEDLINE, Web of Science, Cochrane Controlled Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, SCOPUS and SPORTDiscus using the keywords provided in Supplementary Table 1. The search was narrowed using filters of full text, peer-reviewed, journal articles, human, English language and publication day from November 1985 to January 2021.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (i) randomised controlled trials (RCTs) involving a dietary intervention component that included either a macronutrient or dietary pattern modification, (ii) dietary intake assessment ascertained by validated food frequency questionnaire, multiple-day food diary, or 24-h dietary recall method; (iii) participants including pregnant adult women (aged >18 years, recruited at any point during their pregnancy) and their neonates up to 72 h from birth (for cord blood) and up to 6 months of age (for adiposity); (iv) articles from 1985 to present to capture lifestyle patterns of current times; (v) outcome measure examining fetal insulin secretion by cord blood metabolite analysis and/or infant adiposity. Valid outcome measures included cord blood c-peptide, insulin and/or glucose measured at birth, or infant adiposity measured within 6 months of age using four-compartment or two-compartment model methods, that is, air displacement plethysmography (ADP) or skin fold thickness (SFT).

Exclusion criteria were as follows: (i) research investigating food security or malnutrition; (ii) studies examining a nutritional supplement or supplemental food product; (iii) dietary intervention component inadequately described; (iv) full text article not available in the English language; (v) brief communications, case series, editorials, review studies; (vi) pilot intervention studies without a control group.

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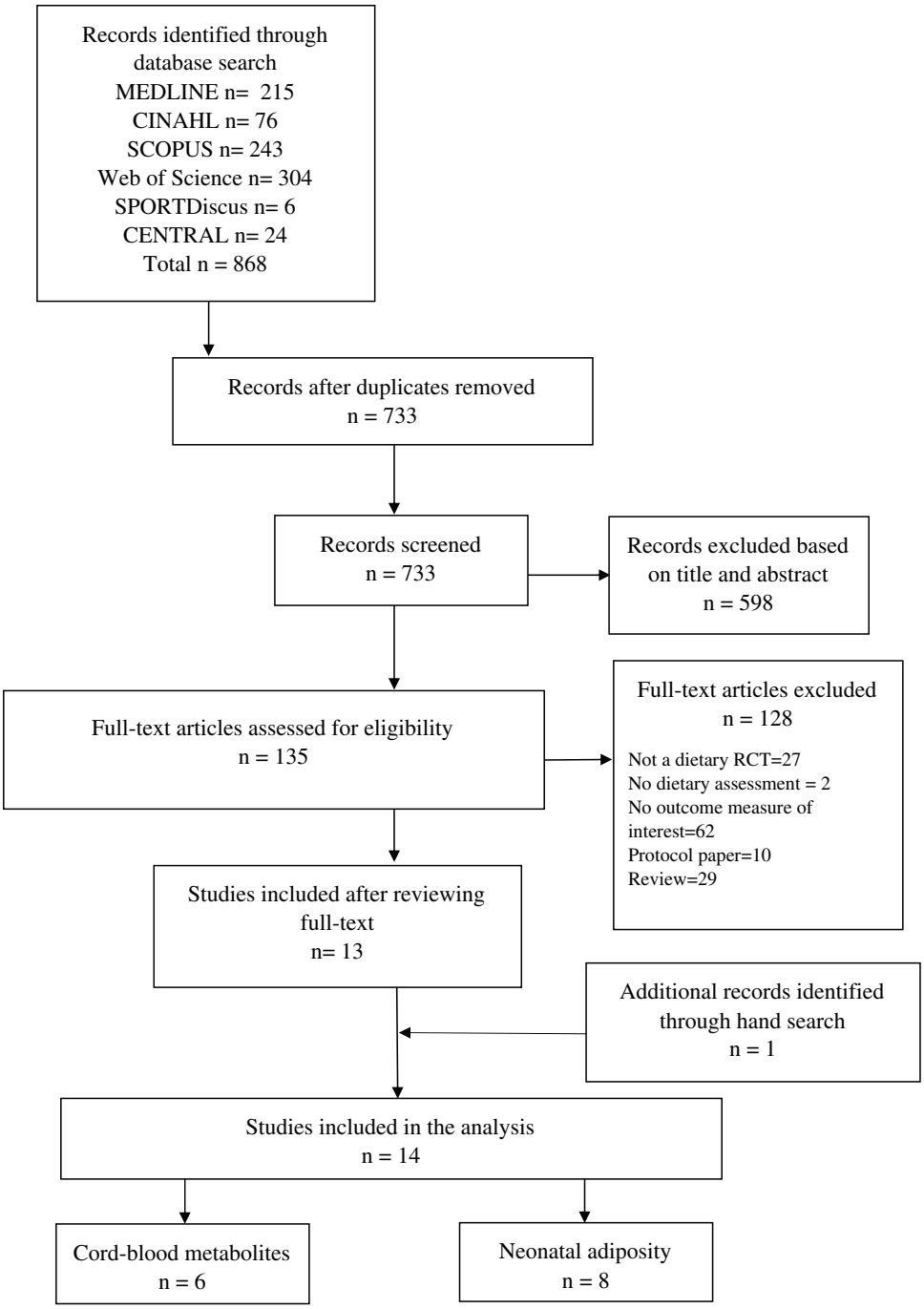

Fig. 1. Flow diagram of literature search.

Study selection

Suitable literature was identified following a three-step screening process (Fig 1). All literature retrieved was collated into Endnote and duplicates removed, then subjected to preliminary (title and abstract) and full-text review. Literature retrieval was performed by the first author (SN). Two independent reviewers (SN and CT) subsequently filtered the identified articles by evaluating titles and abstracts, and subsequently full texts and references based on the inclusion and exclusion criteria. Additional articles identified by hand searching of reference lists from previous review and selected studies were also considered. Any discrepancy in assessment between reviewers was resolved through discussion and rechecking of the full text.

Data extraction

Data were extracted from the included studies in the following domains: country; author; year; study design; number of participants; study groups; participant characteristics (maternal age, BMI, gestational age, gestational weight gain, neonatal birth weight and prevalence of large-for-gestational age); primary outcomes; intervention protocol including intervention content and compliance assessment, timing, outcome measure of interest and study findings. Due to the heterogeneity of populations included in RCTs, results from women with GDM, BMI $\geq 25\ kg/m^2$, and 'healthy' populations were reported separately. Primary outcomes were reported as mean differences between groups (SD) and median (interquartile range), or relative risk if not otherwise

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available. Where mean differences were not reported in the manuscripts, between group differences were calculated using pooled standard deviations.[26] In the instance where all data from included articles was not available, authors were contacted to obtain missing data.

Assessment of reporting quality

Risk of bias was assessed using the Cochrane Collaboration's bias risk assessment tool, where bias was classified into six domains: selection, performance, detection, attrition, reporting and other bias.[27] The 'other' domain referred to dietary intervention compliance, which was classified as low risk when the study design included compliance measures to evaluate participant adherence to assigned dietary intervention. Examples of low compliance bias included telephone or face-to-face dietary review sessions throughout the intervention period, and validated forms of dietary assessments by 24-h food recall or 3-day food diaries. No dietary follow up, low participant adherence or the intervention group not achieving the intended dietary change was rated as a high risk of compliance bias.

Results

Study selection

The number of identified studies is shown in the flow diagram of the literature search in Fig. 1. Titles of 868 articles were found from the search result and 733 were retained after removal of duplicates. Among the 733 that were screened for title and abstract, 135 articles were subjected to full text revision. Articles excluded were not dietary RCTs, did not provide an assessment of the outcome measures of interest, were a protocol paper or review article.

A total of 14 articles from 11 RCTs involving 3614 pregnant women were included. The main characteristics from the included studies are summarised in Table 1. Five studies recruited women in their first trimester with a BMI ≥ 25 kg/m^2.[28–32] Mean participant BMI for these studies ranged between 28.0 and 34.4 kg/m^2, which was reported pre-pregnancy[28,31] or from first-trimester body weight.[29,30,32] In the DALI study women were selected with a pre-pregnancy BMI ≥ 29 kg/m^2,[33] and UPBEAT study, participants had a pre-pregnancy BMI ≥ 30 kg/m^2.[34,35] Women with a previous infant born weighing > 4 kg were recruited for one study (mean BMI 26.5–27.2 kg/m^2 measured in the first trimester).[36–38] Kizirian *et al.*[39] included women with at least one risk factors for GDM. Two studies recruited women diagnosed with GDM.[40,41] Among the remaining 12 studies, women were recruited in the first trimester and the prevalence of GDM ranged from 2 to 41%.[28–39]

Characteristics of interventions

The intervention characteristics are summarised in Table 3.

Intervention delivery

In five studies, the intervention was provided over between two and five individual dietitian- or nutritionist-led sessions.[29–31,36–38,41] Dietary interventions included home-based counselling to reduce sugar consumption alongside docosahexaenoic acid supplementation (2 × 2 factorial design),[29] eucaloric low GI diet,[34,35,36–39] eucaloric low GI diet versus a low fat diet,[32] low glycaemic load (GL) diet with a participant-driven mobile app[30]; calorie-restricted diet (30% restricted),[40] modestly lower carbohydrate diet (135 g/day)[41]; and the DASH diet.[31] Two studies included one-on-one motivational interviewing techniques with participants to facilitate behaviour change for weight management.[28,33] The UPBEAT study involved eight weekly health-trainer led sessions on reducing dietary GL without restricting dietary energy intake.[34,35] Compliance checks in addition to study visits were food diaries[39,40] or 24-h food recall,[28,39,41] telephone interviews,[30,31,33–35] and a logbook with weekly goals in one study.[34,35]

Comparison group

Most studies described control groups as receiving usual care that included standard periodic antenatal visits and referral for medical care as indicated (i.e. following GDM diagnosis).[28,29,31,33–38] Among them, two studies specified providing nutrition advice to the control group as a part of routine care in alignment with national guidelines.[28,29] Five studies compared two dietary interventions where the intensity of the treatment was similar between both groups. These included a low GL vs non-low GL dietary intervention,[30] modestly lower- vs moderate-carbohydrate diet,[41] low GI vs high fibre, higher GI,[39] energy-restricted and non-energy restricted diet,[40] and a low GI vs a low fat diet.[32]

Effects of interventions on dietary intake

Change in dietary intake or behaviour at the end of the intervention are described in Table 3. Women receiving the telehealth-delivered behavioural intervention for weight management in the GLOW trial reported lower energy intake and a lower incidence of excess gestational weight gain (intervention: 41% vs control: 66%, $P < 0.001$).[28] In the DALI trial,[42] the intervention resulted in lower intake of sugar drinks, fat, and carbohydrate, as well as reduced portion sizes, sedentary time, and weight gain. In the GI Baby 4 RCT,[39] the Low GI intervention group had a significantly lower dietary GI, while there was no difference in energy and other nutrients. In the MOM FIT RCT, the intervention group presented with significantly higher Dixon DASH and Fung DASH scores, and higher HEI 2010 scores indicating compliance to the prescribed DASH diet.[31] In the ROLO study, the intervention group was shown to have a significantly lower dietary GI, GL and percentage energy from carbohydrates.[36,38,43] The study intended to provide eucaloric diets, however, the intervention group had lower energy intake in trimesters two and three. Compared to the control, intervention group from the UPBEAT study reported lower dietary GL, GI, total energy intake, total percentage energy from fat, saturated fat, and high percentage energy intake of protein.[34,35] Rhodes *et al.*[32] reported significantly lower dietary GI and GL in the Low GL intervention group. However, there was no significant difference in dietary fat (as a percentage of energy intake) when compared against the 'Low Fat' control group. Zhang *et al.*[30] showed no significant difference between study groups for dietary GI, however, a total reduction in GL, energy, and carbohydrate intake was observed in both groups over the duration of the study.

The following studies did not achieve the intended dietary change. The moderately energy restricted intervention by Rae *et al.*[40] indicated no significant difference between groups for total energy intake. In the moderately lower carbohydrate intervention study by Mijatovic *et al.*,[41] the intervention group had significantly lower total energy, carbohydrate and protein intake. However, groups did not vary in percentage of dietary energy from carbohydrate, protein, fat, GI, GL, and total sugar, starch and fibre. Only 20% of participants in the intervention group were reported meeting the target carbohydrate intake compared with 65% in

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the control group. Garmendia *et al.*[29] did not provide a post-intervention comparison of participant dietary intake in the main study findings. Adherence to the lifestyle intervention was defined as attendance to dietary counselling sessions, for which overall attendance was 69% and 31% attended all sessions.

Neonatal outcomes for each intervention

Cord blood c-peptide, insulin, and glucose

Six of the included studies examined neonatal cord blood. Among them, c-peptide was measured in five studies,[28,30,33,34,36] insulin was measured in three studies,[28,29,34] and four studies reported glucose.[28,29,33,34]

In two studies which delivered a behaviour change intervention to facilitate healthy eating and physical activity for appropriate weight gain, there was no significant difference between groups for cord blood c-peptide, glucose[33] or insulin.[28] Garmendia *et al.*[29] found no significant difference in cord blood glucose and insulin between participants who received home-based dietary counselling to reduce sugar consumption and controls who received no dietary education. In the RCT by Zhang *et al.*,[30] when compared to a dietitian-prepared control diet, the low GL intervention had no significant effect on neonatal cord blood c-peptide. In the secondary analysis from the UK UPBEAT low GI study,[34] there was no significant difference between groups in cord blood insulin or c-peptide. Similarly, the Irish ROLO study found no significant difference in median cord blood c-peptide among participants who received a eucaloric low GI diet provided over three dietitian-led education sessions.[36]

Neonatal adiposity

Eight of the included studies examined neonatal adiposity. Among them, two studies measured SFT at delivery,[32,37] two studies used ADP at delivery,[31,41] two studies measured SFT at 6 months of age,[35,38] and one study used ADP at both delivery and 6 months of age.[39]

Among the four studies that investigated a low GL dietary intervention, the UPBEAT UK RCT, showed a reduction in subscapular SFT at 6 months of age (mean difference −0.38 mm (−0.70 to −0.06), $P = 0.021$), but not triceps SFT.[35] There were no significant associations between the intervention and adiposity outcomes in the ROLO low GI study,[37,38] GI Baby 4 study[39]; MOM FIT DASH dietary intervention[31]; the MAMI 1 modestly lower carbohydrate intervention,[41] moderately energy restricted diet[40] and pilot low GL RCT.[32]

Quality assessment and Risk of Bias

Based on the Cochrane risk of bias assessment tool,[27] the majority of the included studies had a low risk of selection bias due to randomisation and blinded allocation to treatment groups[28–40] (Supplementary Table 2).

Due to the natural of dietary intervention studies, true binding of participants is not feasible. Performance bias also refers to personal involved in delivering the intervention. A low risk of performance bias was suggested in the four studies where the intervention and comparison group were provided with matched intensity.[30,39–41] These studies did not inform participants on their intervention arm. A high risk of performance bias was identified in six studies where the control group received standard antenatal care and specific dietary input was not explicitly described.[28,29,31,33–38]

Most of the included studies reported blinding for outcome assessments (neonatal cord blood analyses and adiposity).[28–39] Blinding during SFT assessments was unclear in one study.[40]

A low risk of attention bias was identified in thirteen studies that used intention-to-treat analysis and adequately described participant withdrawals.[28–39,41] There was a high risk for attention bias in one study where missing data or drop-outs were not reported.[40] There was a low risk of reporting bias in 11 studies[28–33,35–41] which reported all present outcomes from their protocol. One study did not specifically report cord blood insulin and c-peptide outcomes by intervention groups and the authors were contacted for these data, from which the unpublished results are included in Table 2.[34] A low risk of compliance bias was identified in 12 studies which provided multiple points of participant contact and dietary assessments to ensure the intervention was adequately followed.[28–30,34–39,41]

The dietary assessment tool used by Harreiter *et al.*[33] introduced a potential risk of compliance bias; although there was frequent participant contact with a personal lifestyle coach as well as telephone contact, dietary assessments were self-reported according to a short (12-item) questionnaire and not analysed for nutritional intakes. The analysis was also not appropriate to compare adiposity outcomes due to low subject number. The UPBEAT RCT was considered to be low risk for compliance bias, however, it should be noted that the involvement of any dietitian in the control group by standard antenatal referral pathways was not reported although suggested to be minimal.[34,35] Four studies which reported non-significant differences between groups for the intended dietary change at the end of the intervention received an overall 'high' risk for other bias.[29,32,40,41] Although reporting no differences between intervention groups, Zhang[30] indicated a net effect of both study arms on dietary GI.

Discussion

Principal findings

This review aimed to systematically examine the effect of maternal diet on fetal hyperinsulinaemia measured at birth. Due to limited data assessing cord blood insulin or c-peptide (to indicate fetal hyperinsulinaemia), we also included neonatal adiposity as a surrogate marker for *in utero* hyperinsulinaemia. To our knowledge, this is the only review published in the last 5 years to summarise experimental evidence on the impact of maternal diet on fetal insulin metabolism and neonatal (up until 6 months of age) adiposity.

The main results from the included studies do not show any effect of an intervention on neonatal cord blood insulin, c-peptide, or glucose. Among the studies that measured neonatal adiposity, the only intervention that showed a significant reduction in adiposity was the Low GL diet from the UPBEAT study (subscapular SFT −0.38 mm, $P = 0.021$, subscapular SFT z-score −0.26, $P = 0.031$).[35] There was a trend toward improved neonatal adiposity outcomes in the ROLO study (low GI intervention)[37] and DASH diet study.[31]

From the studies which showed no effect of the intended dietary intervention on the outcomes examined in this review, it was noteworthy that the majority of these did not achieve all aspects of the expected dietary change,[30,32,40,41] or did not report follow up dietary assessment information[29] (Table 3). Further, two studies were pilot studies with small participant group numbers, suggesting inadequate statistical power to detect differences between groups in

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Table 2. Study characteristics and results from randomised controlled trials

First author, year of publication, trial name	Study design, country, population, primary outcome	Intervention period	Intervention (I) and control (C) groups	Subjects (-withdrawals)	Participant characteristics						Outcome measure of interest Difference between groups (mean difference, 95% CI)
					Age (years)	BMI	GDM (%) n/n requiring insulin treatment¶¶	Gestational age at delivery (week)	Gestational weight gain (kg)	Birth weight (g) (% LGA)	
(A) Participants with diagnosed GDM											
Rae *et al.*[40]	RCT, Australia Pregnant women with confirmed GDM Maternal insulin therapy, macrosomia incidence	GDM diagnosis (≤ 35 weeks) to delivery	I: Moderate 30% dietary energy restriction (1590–1776 kcal/day) C: Non-energy restricted diabetes diet (2010–2220 kcal/day) Both: Standard treatment including diabetes education, control of hyperglycaemia, fetal and maternal surveillance.	I:66 C:58	I:30.2 C:30.6	I: 37.9 ± 0.7 C: 38.0 ± 0.7	I: 12/66 C: 10/58	I: 37.8 ± 0.3 C: 37.6 ± 0.2	I: 11.6 ± 1.3 C: 9.7 ± 1.5	I: 3461 (28.8) C: 3267 ± 96 (24.6)	SFT-4, 5 days I – C: Subscapular (mm): 0.0 (−0.04–0.04) Suprailiac (mm): 0.3 (0.26–0.34) Triceps (mm): 0.0 (−0.04–0.04) Abdominal (mm): 0.2 (0.15–0.25)
Mijatovic *et al.* MAMI 1[41]	RCT, Australia Pregnant women with confirmed GDM Blood ketone level	24–32 weeks to delivery	I: Modestly lower carbohydrate diet of 135 g carbohydrate per day, without energy restriction. C: Routine care carbohydrate range of 180–200 g/day.	I: 24 (−4) (7 ADP) C: 22 (−8) (8 ADP)	I: 32.5 ± 0.9 C: 34.2 ± 0.9	I: 25.8 ± 1.0 C: 27.8 ± 1.5	I: 14/24 C: 12/21	I: 38.7 ± 0.2 C: 38.6 ± 0.2	I: 10.9 ± 0.9 C: 8.2 ± 1.5	I: 3125 ± 101 (0) C: 3278 ± 79 (4.8)	ADP, delivery I – C: FM (%): −2.9 (−4.76, −1.04)
(B) Participants with BMI ≥ 25 kg/m^2											
Ferrara *et al.* GLOW[28]	Multi-centre RCT, USA Pregnant women from antenatal and medical clinics with pre-pregnancy BMI 25–40 kg/m^2 Excess gestational weight gain	8–15 weeks to delivery	I: Up to 13 × dietitian-delivered telehealth intervention with nutrition and physical activity behaviour change advice. C: Standard antenatal care including periodic health education newsletters, on recommended weight gain, healthy eating, and physical activity in pregnancy.	I: 199 C: 195	I: 32.4 ± 4.1 C: 32.6 ± 4.3	I: 29.3 ± 3.4 C: 29.4 ± 3.8	I: 16 (8) C: 16 (8)	I:39.2 ± 1.8 C:39.0 ± 1.8	I: 10.2 ± 5.6 C: 12.4 ± 5.3	I: 3376 ± 541 (12) C: 3384 ± 507 (15)	Cord blood c-peptide, insulin, glucose I – C: c-peptide (ng/ml): −0.1 (−0.19 to −0.01) Insulin (pmol/l): 1.5 (−15.29–18.29) Glucose (mmol/l): 0.1 (−0.35–0.55)
Garmendia *et al.* MIGHT[29]	2 × 2 factorial RCT, Chile Pregnant women BMI ≥ 25 kg/m^2 at first antenatal visit GDM, macrosomia, cord blood insulin	8–15 weeks to delivery	I_1: Home-based dietary counselling and 800 mg DHA supplementation I_2: 800 mg DHA supplementation I_3: Home-based dietary counselling and 200 mg DHA supplementation I_4: 200 mg DHA supplementation	I_1: 250 (−59) I_2: 252 (−80) I_3: 249 (−54) I_4: 251 (−79)	I_1: 28.4 ± 5.7 I_2: 27.3 ± 5.9 I_3: 27.6 ± 5.6 I_4: 28.1 ± 5.7	I_1: 32.1 ± 4.8 I_2: 32.9 ± 4.7 I_3: 32.0 ± 4.7 I_4: 32.3 ± 4.4	I_1: 21.0 (41) I_2: 20.1 (40) I_3: 18.9 (39) I_4: 20.9 (41)	Not reported	I_1: 9.5 ± 6.2 I_2: 9.0 ± 5.5 I_3: 9.9 ± 6.1 I_4: 9.2 ± 6.3	I_1: 3424 ± 552 (25.9) I_2: 3435 ± 573 (26.3) I_3: 3359 ± 596 (25.0) I_4: 3393 ± 581 (24.8)	Cord blood glucose, insulin I_1 and I_3 vs I_2 and I_4 (RR, 95% CI): Glucose (mg/dl): 0.04 (−0.01 to −0.10 Insulin (μU/ml): 0.01 (−0.15–0.17)
Harreiter *et al.* DALI[42]	Multi-centre 2×(2 × 2) factorial RCT, Europe (nine centres) Pregnant women with a BMI ≥ 29 kg/m^2 GDM	<20 weeks to delivery	I: Healthy eating (with or without physical activity intervention): 5 × individual lifestyle coach advice to reduce sugar and simple carbohydrate and fat intake, increase protein and fibre intake. Telephone and email support throughout. C: Usual care from midwife or obstetrician during pregnancy	I: 221 C: 215 Secondary analysis	I: 32.2 ± 5.4 C: 31.7 ± 5.3	I: 34.6 ± 4.1 C: 34.4 ± 3.8	I: 32 (19.4) C: 35 (20.2)	I: 39.5 ± 2.6 C: 39.6 ± 1.6	I: 7.0 ± 4.4 C: 8.5 ± 4.7	I: 3477 ± 574 (12.5) C: 3494 ± 524 (15.2)	Cord blood c-peptide, glucose I – C: c-peptide (ng/ml): 0.03 (−0.06–0.12) Glucose (mmol/l): −0.3 (−0.06–0.12)

Table 2. (*Continued*)

Patel *et al.* UPBEAT[35]	Multi-centre RCT, UK Pregnant women BMI ≥ 30 kg/m^2 GDM, LGA incidence	15–18 weeks to delivery	I: Complex behavioural intervention with low GL and reduced SFA dietary advice. Weekly health trainer-led sessions C: Usual antenatal care and recommended dietary and physical activity advice through UK health care pathways	I: 342 C: 356	I: 31.3 ± 5.0 C: 31.0 ± 5.6	I: 36.2 ± 5.0 C: 36.3 ± 4.7	I: 97 (28.9) C: 93 (26.9)	I: 39.5 ± 2.0 C: 39.5 ± 2.4	I:6.9 ± 4.7 C:7.8 ± 4.4	I: 3479 ± 529 (8.8) C: 3437 ± 604 (7.6)	SFT-4, 6 months I – C: Subscapular *z*-score: −0.26 (−049 to −0.02) Subscapular (mm): −0.38 (−0.70 to −0.06) Triceps *z*-score: −0.14 (−0.38–0.10) Triceps (mm) −0.22 (−0.64–0.20) Sum (mm): −0.63 (−1.30–0.04)
Patel *et al.* UPBEAT[34]				I: 169 C: 174 Secondary analysis	I: 31.0 (28.0–35.0) C: 31.0 (27.0–35.0)	I: 35.5 (33.0–39.1) C: 35.7 (33.0–38.5)	I: 59 (34.9) C: 52 (29.9)	I: 39.7 (38.7–40.7) C: 40.0 (38.7–41.0)	I:6.9 ± 4.3 C:8.0 ± 3.8	I: 3510 (3220–3790) C: 3590 (3190–3860) (LGA not available)	Cord blood c-peptide, insulin, glucose I – C: Insulin (U/ml): −0.135 (−0.000299–0.271) c-peptide (g/ml): 0.0329 (−0.0459–0.112)
Rhodes *et al.*[32]	Pilot RCT, USA Pregnant women BMI 25–45 kg/m^2 Infant birth weight *z*-score	13–28 weeks to delivery	Low GL: Low GI carbohydrates (45% carbohydrate, 35% fat, 20% protein) Low fat: Consistent with American Dietetic Association recommendations (55% carbohydrate, 25% fat, 20% protein, low-saturated-fat, high complex carbohydrate)	Low GL: 24 (−3) Low fat: 21 (−5)	Low GL: 33.7 ± 3.9 Low fat: 33.2 ± 3.7	Low GL: 32.1 ± 4.6 Low fat: 31.2 ± 3.1	Low GL: 0 (0)¶ Low fat: 1 (4)¶	Low GI: 39.3 ± 1.1 Low fat: 37.9 ± 3.1	I:6.4 ± 4.5 C:6.9 ± 4.2	Low GI: 3507 ± 412 (8) Low fat: 3133 ± 671 (14)	SFT-4, delivery Low GL-Low fat: Subscapular (mm): −0.4 (−0.97, 0.17) Triceps (mm): −0.5 (−1.01, 0.01) Suprailiac (mm): −0.1 (−0.67, 0.47) Thigh (mm): −0.3 (−1.09, 0.49)
Van Horn *et al.* MOM FIT[31]	RCT, USA Pre-pregnancy BMI 25–40 kg/m^2 Gestational weight gain	16 weeks to delivery	I: Dietary approaches to stop hypertension diet and physical activity intervention with individualised and group coaching with a smartphone application was used for self-monitoring. C: Usual antenatal care	I:140 C:141	I: 33 ± 4 C:34 ± 4	I:31 ± 4 C:31 ± 4	I: 7 (5.3) C: 9 (7.1)	I:39 ± 2 C: 39 ± 2	I:10 ± 6 C:12 ± 6	I: 3244 ± 489 (5.8) C: 3213 ± 524 (8.8)	ADP, <72 h I – C: FM (%): −0.7 (−1.71–0.31)
Zhang *et al.*[30]	RCT, China Pregnant women BMI ≥ 25 kg/m^2 Maternal and neonatal insulin resistance	16 weeks to delivery	I: Low GL Individualised dietitian-prepared diet plan and mobile app instructions C: Individualised dietitian-prepared diet plan to meet standard nutrition goals Both: 3 × dietitian consultation incorporated with routine antenatal care visits until delivery	I: 200 (−17) C: 200 (−14)	I: 28.0 ± 3.7 C: 28.1 ± 3.6	I: 28.0 ± 3.0 C: 28.4 ± 3.0	I: 45 (22.5) C: 43 (21.5)	I: 39.7 ± 1.2 C: 39.8 ± 1.7	I: 9.6 ± 7.4 C: 11.2 ± 63	I:3514 ± 522 C: 3453 ± 527 (LGA not available)	Cord blood c-peptide I – C: c-peptide (ng/ml): 0.01 (−0.15–0.17)
(C) Participants with other pre-existing risk factor for fetal hyperinsulinaemia											
Donnelly *et al.* ROLO[37]	Nested case-control RCT, Ireland, Pregnant women with previous macrosomia (infant born > 4 kg) Infant birth weight	16 weeks to delivery	I: Eucaloric low GI diet, 3 × dietitian sessions including dietary education and written information (14, 28, and 34 weeks gestation) C: Usual antenatal care with no dietary advice	I: 126 C: 139	I: 32.7 ± 3.8 C: 32.1 ± 4.6	I: 27.2 ± 4.9	I: 7/350 (2) C: 9/371 (2)†	40 ± 2.7†	I: 14.1 ± 11.1 C:13.8 ± 4.5	I: 4034 ± 510 (51% > 400 g) C: 4006 ± 497 (51% >400 g)†	SFT-4, <72 h from delivery I – C: Subscapular (mm): −0.04 (−0.41, 0.33) Triceps (mm): −0.09 (−0.45, 0.27) Biceps (mm): −0.1 (−0.46, 0.26) Leg (mm): 0.08 (−0.34, 0.50) Sum SFT (mm): −1.6 (−4.47, 1.27)
Horan *et al.* ROLO[38]				I: 138 C: 142	I: 33.2 ± 3.8 C: 33.0 ± 4.1	I: 26.0 ± 4.3 C: 26.2 ± 4.5			I: 12.2 ± 4.4 C: 13.7 ± 4.9†		SFT-4, 6 months I – C: Subscapular (*z*-score): 0.32 (0.05, 0.59) Triceps (*z*-score): 0.098 (−0.17, 0.36) Biceps (mm): −0.01 (−0.48, 0.46) Leg (mm): 0.25 (−0.41, 0.91) Sum SFT (mm): 0.85 (−0.53, 2.23)
Walsh *et al.* ROLO[36]				I: 235 C:250 Secondary analysis	I: 32.7 ± 3.8 C: 32.1 ± 4.6‡	I: 27.2 ± 4.9 C: 26.5 ± 4.3‡					Cord blood c-peptide I vs C: (median, IQR): c-peptide (ng/ml): 206.6 (65.7–700.6) vs 206.4 (52.8–731.4), $P = 0.96$

(*Continued*)

Table 2. (*Continued*)

First author, year of publication, trial name	Study design, country, population, primary outcome	Intervention period	Intervention (I) and control (C) groups	Subjects (-withdrawals)	Participant characteristics						Outcome measure of interest Difference between groups (mean difference, 95% CI)
					Age (years)	BMI	GDM (%) n/n requiring insulin treatment¶¶	Gestational age at delivery (week)	Gestational weight gain (kg)	Birth weight (g) (% LGA)	
Kizirian *et al.* GI Baby 4[39]	Pilot prospective follow up RCT, Australia Pregnant women with at least one of the following risk factors: BMI ≥ 30 kg/m^2, age ≥ 35 years, polycystic ovary syndrome, previous GDM or glucose intolerance, previous infant born > 4 kg, first-degree relative with type 2 diabetes, or belonging to an ethnic group with a high prevalence of GDM Infant body composition	12–20 weeks to delivery	Low GI: GI ≤ 50 High fibre: GI 60 Both: 5 × dietitian consultations throughout gestation. Diets matched by macronutrients (15–25% protein, 25–30% fat, 40–45% carbohydrate)	Low GL: 30 High fibre: 29	Low GL: 34.9 ± 0.8 High fibre: 35.5 ± 0.7	Low GL: 25.8 ± 1.0 High fibre: 25.9 ± 1.0	Low GL: 8 (27) High fibre: 9 (31)	Low GL: 39.4 ± 0.3 High fibre: 39.9 ± 0.2	Low GL: 10.6 ± 1.0 High fibre: 10.7 ± 1.0	Low GL: 3400 ± 100 (0.0) High fibre: 3990 ± 200 (6.9)	ADP, delivery, 3 months, and 6 months Low GL vs high fibre: FM (%): Birth: −1.1 (−3.56, 1.36) 3 months: 0.6 (−2.10, 3.30) 6 months: −1.1 (−3.37, 1.17) FM (index): Birth: −0.1 (−0.38, 0.18) 3 months: 0.2 (−0.65, 1.05) 6 months: 0.0 (−0.57, 0.57)

BMI, body mass index; CI, confidence interval; c-peptide, cord blood c-peptide measured on delivery day; DHA, docosahexaenoic acid; FM, estimated fat mass; GI, glycaemic index; GL, glycaemic load; g, grams; h, hour; IQR, interquartile range; LGA, large-for-gestational-age, defined as infants born >90th percentile; SFT-#, skin fold thickness and number of sites.

Study names: DALI, Vitamin D and lifestyle intervention for GDM prevention; GLOW, gestational weight gain and optimal wellness RCT; LIMIT, limiting weight gain in overweight and obese women during pregnancy to improve health outcomes; MAMI 1, macronutrient adjustments in mothers with gestational diabetes study 1; MIGHT, maternal obesity/overweight control through healthy nutrition; MOMFIT, maternal offspring metabolics family intervention trial; ROLO, randomised control trial of low glycaemic index diet in pregnancy; UPBEAT, UK pregnancies better eating and activity trial.

Values reported as mean ± SD, median (IQR) or otherwise indicated.

†Reported from an earlier publication on the same population.

‡Participant demographics reported from Donnelly *et al.*[37] DOI: 10.1111/j.2047-6310.2013.00216.x.

¶Participants with a glycated haemoglobin >6% at 36 weeks gestation.

¶¶Participants treated with insulin in studies that included only women with GDM.

Table 3. Dietary intervention characteristics from randomised controlled trials

First author, year	Monitoring personnel	Main content of the intervention (I) and control (C)	Feedback	Dietary assessment, and compliance measures	Intended change in dietary intake or behaviour achieved
Ferrara *et al.*[28]	Dietitian	I: Telehealth-delivered motivational interviewing behaviour change for weight management (according to IoM guidelines) health eating (e.g. setting goals for eating healthy foods in appropriate portion sizes, total caloric intake, calories from fat), physical activity, and stress management. C: Standard antenatal medical care, seven antenatal visits on average from 7 to 10 weeks' gestation; Periodic health education newsletters, including the Institute of Medicine GWG guidelines, healthy eating, and physical activity information.	13 × weekly individual sessions, followed by optional maintenance telephone sessions.	Printed workbook and personalised graph to track weight gain. 24-h dietary recalls at baseline (8–15 weeks) and 29–38 weeks' gestation.	Change in dietary intake at end of intervention, I-C (mean difference, 95% CI): Energy (kcal/day): −107.3 (−192.2, 22.5; $P = 0.13$) No significant difference between groups for % energy from fat, saturated fat, or unsaturated fat, or physical activity (MET equivalents and self-reported)
Garmendia *et al.*[29]	Nutritionist	I_1 and I_3: Dietary intervention focused on reducing consumption of seven most significant contributors to daily sugar consumption: refined sugar, cookies, processed fruit juices, sugar sweetened yogurt, sugar-sweetened beverages, powdered juices with added sugar, and bread All: Routine antenatal care and nutritional advice according to the national guidelines	3 × sessions throughout pregnancy; game to assess participants' nutritional knowledge and specific personalised advice to address nutrition knowledge deficits.	FFQ (800 items; energy and sugar intake) at baseline and 35–37 weeks visits. Adherence defined as attendance to dietary counselling	Post intervention dietary intake not reported.
Harreiter *et al.*[42]	Lifestyle coach	I: Lifestyle coach delivered motivational interviewing on healthy eating (with or without physical activity intervention). Advice to reduce sugar and simple carbohydrate and fat intake, increase protein and fibre intake, and regulate calorie intake by reducing portion sizes. C: Usual antenatal care.	5 × individual lifestyle coach sessions 4 × telephone and email support throughout. Toolkit with behaviour change materials and participant manual with weight management information. Coaching sessions evaluated by motivational interviewing trainer.	Self-reported 12-item dietary questionnaire at <20, 24–28, and 35–37 weeks' gestation.	Change in dietary intake at 35–37 weeks', I-C (mean difference, 95% CI): Sugar drinks (n/week): −3.3 (−5.1, −1.4; $P < 0.001$) Fat (n/week): −1.5, (−2.8,−0.3; $P < 0.05$) Carbohydrates (n/week): −6.2, (−11.6, −0.9; $P < 0.05$) Portion size (n/week): −3.8 (−6.8, −0.9; $P < 0.01$) Sedentary time (MET hour/week): −1.6 (−3.3; 0.0; $P < 0.05$) Weight gain (kg): −1.5 (22.4; 20.5; $P < 0.01$) No significant difference between groups for fibre, protein, total physical activity, or moderate vigorous physical activity.
Kizirian *et al.*[39]	Dietitian	Low GI: GI ≤ 50 High Fibre: GI 60 Both: Diets matched by macronutrients (15–25% protein, 25–30% fat, 40–45% carbohydrate)	5 × dietitian consultations at 14–20, 18–24, 22–28, 26–32, and 34–36 weeks gestation 3 × mid-study visits (visits 2, 3, and 4) 24-h recalls performed to check dietary compliance (dietary GI was <50 in The Low GI group and >50 in the high fibre group. In the case of non-compliance, suitable alternative foods	3-day food diary × 2 (12–20, 34–36 weeks).	Change in dietary intake at end of intervention, Low GI vs High Fibre (mean ± SEM) GI: 51 ± 1 vs 57 ± 1; $P < 0.001$ No significant difference between groups for energy, protein, total fat, saturated fat, carbohydrate, sugar, starch, fibre, % energy from protein, % energy from fat, % energy from carbohydrate.

(*Continued*)

Table 3. (*Continued*)

First author, year	Monitoring personnel	Main content of the intervention (I) and control (C)	Feedback	Dietary assessment, and compliance measures	Intended change in dietary intake or behaviour achieved
			were encouraged. A selection of recipes was also provided.		
Mijatovic *et al.*[41]	Dietitian	I: Carbohydrate target of 135 g/day without energy restriction C: Carbohydrate target of 180–200 g/day.	3–4 × study visits with usual antenatal care. Pictorial booklet, showing carbohydrate content, a target number of portions, and GI.	3 × 24-h food diary. 3 × 2-day blood ketone diary. 24-h food recall at each study visit to assess compliance.	Change in dietary intake at end of intervention for study completers, I vs C (mean ± SEM): Energy (kJ): 7040 ± 240 vs 8230 ± 320; $P < 0.01$ Carbohydrate (g): 165 ± 7 vs 190 ± 9; $P = 0.04$ Protein (g): 85 ± 4 vs 103 ± 4; $P < 0.01$ No significant difference between groups for sugar, starch, fibre, total fat, saturated fat, long chain omega-3 fatty acids, % energy from protein, % energy from fat, % energy from carbohydrate, GI, and GL.
Patel *et al.*[34,35]	Health trainer (provided study-specific training)	I: Initial one-on-one health trainer-led interview followed by 8 weekly sessions. Dietary advice to decrease dietary GL (exchanging starchy foods with a medium/high GI for those with a lower dietary GI, and restricting the consumption of sugar-sweetened beverages (including fruit juice)), but not to restrict dietary energy intake. Physical activity advice to increase daily step count. C: Standard antenatal care, which may include referral to a dietitian. Authors suggest referral is infrequently implemented and women likely to only be weighed once in the first antenatal visit.	8 × weekly trainer-led sessions (or phone call if not attended) Participant handbook, exercise DVD and pedometer. Logbook for recording weekly goals and steps as assessed by pedometer.	FFQ at 15–18, 27–28, and 34–36 weeks	Change in dietary intake at end of intervention, I vs C (mean difference, 95% CI): GL: −35.34 (−48.00, −22.67; $P < 0.001$ GI (0–100): −3.94 (−4.93, −2.94; $P < 0.001$) Total energy (kcal/day): −354.52 (−505.95, −203.10, $P < 0.001$) Total fat (%E): −2.65 (−3.91, −1.38; $P < 0.001$) Saturated fat (%E): −1.93 (−2.64, −1.22; $P < 0.001$) Protein (%E): 2.70 (1.63, 3.77; $P < 0.001$) No significant difference between groups for carbohydrate, fibre, or exercise (MET; moderate and vigorous physical activity, or walking).
Rae *et al.* 40	Dietitian	I: Moderate 30% dietary energy restriction (1590–1776 kcal/day) C: Non-energy restricted diabetes diet (2010–2220 kcal/day) Both: Standard treatment including diabetes education, control of hyperglycaemia, fetal and maternal surveillance.	Unspecified	3-day food diary × 3 throughout study period.	Change in dietary intake at end of intervention, I vs C (mean ± SEM): Total fat (g): 56 ± 2.0 vs 63 ± 2.4; $P = 0.023$ Total fat (%E): 31 ± 0.7 vs 34 ± 0.7; $P = 0.11$ No significant difference between groups for energy, carbohydrate, or protein.
Rhodes *et al.*[32]	Dietitian	Low GL: Low GI carbohydrates (45% carbohydrate, 35% fat, 20% protein) Low fat: Consistent with American Dietetic Association recommendations (55% carbohydrate, 25% fat, 20% protein, low-saturated-fat, high complex carbohydrate) Both: In-person and phone counselling, structured written guides.	In-person maintenance visits at 2–4-weeks intervals.	24-h diet recall at 32–36 weeks	Change in dietary intake at end of intervention, Low GL vs Low fat (mean ± SD): GI: 51.8 ± 6.9 vs 58.0 ± 4.3; $P = 0.002$ GL (g/1000 kcal): 56.3 ± 15.2 vs 69.1 ± 11.9; $P = 0.005$ Fibre (g/1000 kcal): 16.5 ± 5.0 vs 13.4 ± 4.5; $P = 0.05$ No significant difference between groups for energy, percentage energy from carbohydrate, protein, fat, or saturated fat.
Van Horn *et al.*[31]	Dietitian	I: DASH diet and physical activity intervention with individualised and group coaching with a smartphone application was used for self-monitoring. C: Usual antenatal care	3 × individual dietitian led sessions, and 6 × group counselling by phone or webinar. Telephone, text message prompts, and e-mail reminders to encouraged adherence and website viewing.	24 h diet recall at baseline and 35 weeks.	Change in dietary intake at 35 weeks, I vs C (median, IQR): Dixon DASH score: 4 (3–4) vs 3 (3–4); $P = 0.01$ Fung DASH score:27 (25–30) vs 26 (22–29); $P = 0.005$ HEI 2010 score: 70 (62–77) vs 63 (56–75); $P = 0.002$

Table 3. (*Continued*)

Walsh *et al.*[36], Horan *et al.*[38], and Donnelly *et al.*[43]	Dietitian	I: Eucaloric low GI diet 3 × group sessions (4–6 participants) and written information C: Usual antenatal care with no dietary advice	3 × dietitian education sessions (14, 28, and 34 weeks gestation)	3-day food diaries at each trimester. FFQ at 12 and 28 weeks. Average weekly exercise. Maternal weight recorded at 12, 20, 28, 34, 36, 38, 40 weeks. Subjective dietary adherence based on 5-point Likert-type scale	Change in dietary intake, I vs C (mean ± SD): Trimester 2 energy (kcal/day): 1775.9 ± 396.6 vs 1961.9 ± 376.4; $P < 0.001$ Trimester 3 energy (kcal/day): 1858.0 ± 410.1 vs 2000.1 ± 449.8; $P = 0.009$ Trimester 2 protein (%E): 18.3 ± 3.2 vs 16.4 ± 2.7; $P < 0.001$ Trimester 3 protein (%E): 17.9 ± 3.2 vs 16.6 ± 3.1; $P = 0.001$ Trimester 2 carbohydrate (%E): 48.8 ± 5.7 vs 50.9 ± 5.6; $P = 0.003$ Trimester 3 carbohydrate (%E): 48.6 ± 5.5 vs 50.5 ± 6.2; $P = 0.009$ Trimester 2 GI: 56.2 ± 4.0 vs 57.7 ± 3.8; $P = 0.003$ Trimester 3 GI: 56.2 ± 3.9 vs 57.8 ± 4.1; $P = 0.003$ Trimester 2 GL: 121.5 ± 29.5 vs 143.8 ± 31.2; $P < 0.001$ Trimester 3 GL: 127.1 ± 27.8 vs 146.4 ± 41.6; $P < 0.001$ No significant difference between groups for total fat, saturated fat, monounsaturated fat, and polyunsaturated fat.
Zhang *et al.*[30]	Dietitian	I: Individualised low GL dietary plan with mobile app instructions C: Individualised dietitian-prepared diet plan to meet standard nutrition goals Both: Standard nutrition and physical activity consultation according to the national recommendations of the Chinese Nutrition Society and gestational weight gain advice according to IoM guidelines. Individualise dietary assessment and planning. 3 × dietitian consultation incorporated with routine antenatal care visits until delivery	DietGI mobile app to allow personal tracking of meal and whole day diet GI and GL 3 × dietitian education sessions (16, 24–28, 34–36 weeks) Telephone interview monthly to promote compliance.	24-h food recall at three visits.	Change in dietary intake at end of intervention, I vs C (mean ± SD): Trimester 2 GI: 64.8 ± 9.4 vs 62.8 ± 9.8; $P = 0.05$ Trimester 3 fibre: 11.6 ± 8.0 vs 8.9 ± 5.6; $P = 0.006$ No significant difference between groups for dietary GL, energy, carbohydrate, protein, and fat intake in trimesters 2 and 3. No significant difference in dietary GI for trimester 3.

IoM guidelines: Institute of Medicine guidelines no more than 7 kg for women with pre-pregnancy BMI 25 · 0–29 · 9 kg/m^2 or 5 kg for women with pre-pregnancy BMI 30 · 0 kg/m^2 or higher.
DASH, dietary approaches to stop hypertension; FFQ, food frequency questionnaire; GI, glycaemic index; GL, glycaemic load; h, hour; IQR, interquartile range; SD, standard deviation; SEM, standard error from the mean.

neonatal adiposity.[39,41] Data included from the DALI trial was a secondary analysis, which authors reported was inadequately powered to detect differences in neonatal outcomes.[42]

Low GI dietary interventions are well-recognised as a feasible and effective strategy in the medical nutritional management of GDM.[18] The most recent meta-analysis and systematic review of low GI diets provided to women with GDM clearly demonstrated that these diets improve glycaemic control,[44] which is key for reducing the risk of maternal and neonatal complications.[12] Consistent with findings in our current review, the benefits of a low GI diet appear to exist wider than GDM pregnancies. In a meta-analysis by Zhang *et al.*[45] authors concluded low GI diets provided during healthy pregnancies and to those with GDM were associated with a reduced incidence of infants born large-for-gestational-age, as well as improved maternal fasting and 2-h postprandial glucose levels.

A trend toward reduced adiposity was also observed in the UPBEAT trial during which women with obesity (BMI ≥ 30 kg/m^2) were provided with a low GL intervention. Among participants where over a quarter of the women developed GDM, the intervention was associated with reduced neonatal subscapular SFT.[35] Similarly, the ROLO study showed a trend toward lower neonatal SFTs at delivery.[37] Participants were women with a previous macrosomia pregnancy, but only 2% of the women developed GDM. It is plausible that low GL dietary strategies could improve glycaemic control in women with pre-existing insulin resistance, reducing the risk of fetal over-nutrition. The greater incidence of GDM among participants from the UPBEAT trial may explain significantly better outcomes among the participants who received this specific low GL intervention. This could be interpreted in two ways; women with greater baseline insulin resistance at the beginning of pregnancy have larger capacity to improve metabolic markers following lifestyle changes. Secondly, interventions provided through usual GDM care may have an independent treatment effect on fetal development thereby being additive to low GL dietary advice. Interventions for women with GDM including glucose monitoring, pharmaceutical interventions (oral hypoglycaemics or insulin) and increased obstetric monitoring all aim to reduce the risk of fetal hyperinsulinaemia and related obstetric complications.[12]

A trend towards a lower neonatal body fat percent among women receiving a DASH dietary intervention is consistent with results from the recent systematic review and meta-analysis.[46] Among six studies providing a DASH dietary intervention to pregnant women, the DASH diet was associated with a decreased risk of pre-eclampsia, macrosomia, large-for-gestational-age infants and overall lower ponderal index. Although the DASH diet was found to have a significant lowering effect on maternal fasting plasma glucose, the maternal homeostasis model assessment of insulin resistance was unaffected. Consumption of a DASH diet may improve maternal glucose levels by having a lower glycaemic impact. Improvements in maternal glycaemia may prevent nutrient excess, fetal hyperinsulinaemia and resulting excess growth.[47] This supports findings from our systematic review to suggest that adherence to a glycaemic DASH diet in women with an elevated pre-pregnancy BMI could reduce neonatal adipose development that is associated with the risk of macrosomia and large-for-gestational-age babies.

Despite limited associations between any one type of intervention and neonatal outcomes, our findings point to an important role of dietary education. There were associations between interventions and lower estimated neonatal fat mass percent and SFT in studies that compared a personalised lifestyle intervention to standard antenatal care (no specific nutrition or lifestyle advice).[31,35,37] Common elements from these interventions included dietary personalisation with a dietitian or 'health trainer', written education resources, and multiple points of contact to reinforce the provided advice and promote adherence. However, in studies that provided the comparison group with a similar level of support, for example, personalised meal plan, written resources, compliance checks,[30,39,41] no significant effect of a low GI, low GL, or moderately carbohydrate restricted diet was observed. What this suggests is that personalised dietary advice, including follow up support and goal setting throughout gestation, may be just as, if not more, important than the specific dietary intervention alone. From the included studies, the interventions did not differ significantly in terms of practical dietary changes recommended (i.e. reduce sugar, increase fruit and vegetable intake, unrefined carbohydrate choices), making it difficult to distinguish any specific effect of one dietary change. These findings also highlight that general healthy eating education may be overlooked during usual antenatal care, particularly for women who carry risk factors for insulin resistance but are not diagnosed with GDM. Individualised advice allows women to understand their risk factors, respond to feedback throughout pregnancy, set measurable goals and make realistic behavioural adjustments. Communicating health advice within the context of an individual's lifestyle is key to supporting healthy behaviours which could impact maternal, infant, and life-long family metabolic health.[48]

A further explanation for the lack of associations between any of the included dietary interventions and cord blood metabolites (c-peptide, insulin, glucose) may be due to challenges associated with the metabolic analyses used. Although umbilical cord blood is considered one of the most useful samples in neonates instead of early peripheral blood examination,[49] insulin measurement has limitations since degradation increases in the presence of slight haemolysis.[50] While c-peptide is a more stable and useful marker of fetal metabolic exposures,[15] no difference in c-peptide between intervention and control groups was observed in any of the five studies with this outcome measure. This suggests that these biomarkers may not be suitable to determine the specific metabolic impact of maternal dietary modifications in women without gestational hyperglycaemia.

Previous research suggests adipokines may be a more sensitive marker of placental-fetal nutrient transfer. In the HAPO study, lower cord blood levels of adiponectin and c-reactive protein were associated with a higher neonatal adiposity.[51] Adiponectin has been negatively associated with birth weight and estimated percentage fat mass.[51] Leptin has also been linked to adipose development and insulin metabolism,[52] which was identified in a secondary analysis from the ROLO study, as being associated with greater neonatal adiposity, while fetal c-peptide was not significant after adjustments.[43]

Strengths and Limitations

A strength of this review is the inclusion of studies from diverse populations of pregnant women from varying cultural backgrounds. Studies reviewed included pregnant women with varying risk factors including GDM and obesity. The potential for replication bias introduced from five individual references from two study populations (UPBEAT,[34,35] ROLO[36–38]) is a limitation. Heterogeneity among the sampled participants may also limit the practical application of diet advice to specific populations. It is also possible that participant heterogeneity may have confounded a specific effect of individual dietary changes.

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Among the included studies, maternal insulin resistance was not exclusively examined in the recruitment criteria. This is important because maternal insulin resistance before pregnancy is a fundamental determinant of placental-fetal metabolism, nutrition status, and subsequent fetal development.[1] Variability in the prevalence of GDM diagnosis among the participants in the included studies is a limitation. GDM diagnosis and treatment has the potential to influence lifestyle behaviours through additional monitoring and interventions. A higher prevalence of GDM in the included studies where a significant effect of the intervention on neonatal adiposity was observed limits our interpretation. Also noteworthy is the possibility for confounding obstetric variables such as time in labour, placental attachment, cord blood clamping to influence cord blood analysis.

Recommendations for future research

Future research investigating the impact of lifestyle interventions should consider a multi-modal approach to address maternal insulin resistance syndrome as it impacts placental-fetal metabolism. This means dietary factors must be considered alongside other environmental determinants such as physical activity, gestational weight gain, sleep quality, smoking and maternal stress.[53] To reduce heterogeneity from lifestyle factors within studies, RCTs may consider a multi-level intervention design to provide women relevant, personalised interventions based on pre-pregnancy behaviours.

Dietary intervention studies require specific dietary prescriptions that are measurable and repeatable in clinical practice. This means that research examining maternal dietary intake requires thorough, valid dietary assessments, such as 3-day food diaries or the use of diet tracking apps throughout gestation with attention to macronutrient intake, types of carbohydrates and micronutrient adequacy. We recommend that future studies examining neonatal metabolic outcomes should be assessed alongside first trimester maternal insulin resistance to better understand early gestation developmental impacts among mothers with varying patterns of gestational hyperinsulinaemia.[54] Consistent methodology for examining neonatal metabolites at birth must be considered. This includes accounting for technical variables such as neonatal cord clamping and time in labour.

Conclusions

This systematic review indicates gaps in experimental evidence to demonstrate a specific relationship between dietary interventions during pregnancy to prevent subclinical fetal hyperinsulinaemia, measured by cord-blood metabolites and neonatal adiposity. Limited evidence from RCTs suggests dietary strategies that are known to improve glycaemic control in GDM pregnancies may have a protective effect against excess adiposity by a similar mechanism. Additionally, findings from RCTs suggest that antenatal dietary counselling appears to have a protective effect and should be offered to all pregnant women with overweight or obesity. The reviewed studies identified challenges with dietary research where an impact on sub-clinical metabolic changes may be confounded by lifestyle factors and participant adherence issues. Future large dietary RCTs should consider a multi-modal design to explore the specific effect of dietary modification, particularly in the context of environmental risk factors for maternal insulin resistance such as physical activity, stress and sleep. Further research is needed to confirm if specific nutrient modifications, independent of energy balance, in non-GDM pregnancies reduce the risk of fetal hyperinsulinaemia and fetal overgrowth in women with underlying insulin resistance.

Supplemental Tables. To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174421000623

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